LEADING ARTICLE

FRUCTOSAMINE AND DIABETES

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One of the more controversial issues in the field of diabetology is whether near-normal blood glucose protects against long-term vascular complications. This is testified by the need for the on-going Diabetes Control and Complications Trial (DCCT) (1) designed to restudy the subject in IDDM.

In the meantime watching blood glucose leveis remains a major preoccupation of those looking after diabetics and patients themselves. The use of glycated haemoglobin as an index of integrated glycaemic control over a period of 2-3 months has to some extent diminished the emphasis placed on isolated blood glucose readings, especially in the stable NIDDM s Its advent in the 1970s led, not surprisingly, to the discovery that many other proteins are similarly glycated by a non-enzymic post-translational reaction to form an intermediate Schiff base which is then transformed by Amadori rearrangement into a stable ketoamine. This ketoamine end-product of protein glycation is fructosamine, the trivial name for 1-amino-1-deoxyfructose. Like glycated haemoglobin the amount of fructosamine is increased in a setting of persistent hyperglycaemia. The difference is that, because of the more rapid turn-over of circulating proteins, fructosamine reflects mean blood glucose concentration over a shorter period of 2-3 weeks.

There are at least five different ways of measuring fructosamine: (i) Phenylhydrazine Procedure (2), (ii) Furosine Procedure (3), (iii) Affinity Chromatography (4), (iv) 2-Thiobarbituric Acid (TBA) Colorimetric Procedure (5), and (v) Nitroblue Tetrazolium (NBT) Procedure (6). This last method is the subject of a paper in this issue of the SMJ.

Fructosamines are reductants under alkaline conditions. This property forms the basis for the NBT procedure in which the dye NBT is reduced to formazane which is then measured spectrophotometrically. The rate of formation of formazane is directly proportional to the fructosamine concentration. The results are expressed as mmol/L of desoxymorpholino-fructose (DMF) which is the synthetic ketoamine used as primary standard.

The NBT method is fast, simple, cheap in terms of reagents, reproducible and can be easily automated (7). A major drawback is that the test does not specifically measure glycated proteins (8). Between 25 and 60% of the reducing activity of fructosamine was found to be not due to non-enzymic glycation of proteins. Another problem relates to the effect of serum albumin on fructosamine values. Approximately 55% of measured fructosamine involves albumin (9). Its value is reported to be unaffected by albumin concentration above 3.0 G/L (9). Others (10) reported an effect on fructosamine over a wider range of serum albumin. Staley (11) pointed out that in the glycation of proteins, the molar concentration of reactive lysine groups of proteins is always in excess of that of carbonyl groups of glucose. The rate-limiting step is therefore the glucose concentration. Hence hypoalbuminaemia per se does not necessarily lower fructosamine concentration. Shortened half-life of proteins, as opposed to decreased synthesis, for obvious reasons, will affect fructosamine concentration. Nevertheless, various correcting factors for low albumin have been proposed (10, 12). The standardisation of the assay also presents some problems. This is because the standard, DMF, is prepared in a solution of albumin, the type and source of which affects its reactivity with NBT (7).

Currently, besides the NBT method, affinity chromatography using phenylboronic acid is the other method of fructosamine measurement that has potential for routine use by virtue of its simplicity and reported good precision (13).

The clinical usefulness of fructosamine stems from the observation that it can distinguish between normal and well-controlled diabetics from poorly-controlled patients whether it is measured by the NBT method (6), TBA method (5) or affinity chromatography (4). Further support is based on the reasonably good correlation between fructosamine and glycated haemoglobin (6) though there are exceptions (14). Good correlation is also seen between mean daily blood glucose and frustosamine (15). Within-run and day-to-day coefficients of variations (CVs) with the NBT method is typically in the range of 2-7% (16). It is gratifying that the paper in this issue of the SMJ reports CVs between 2.8 and 4.3%

These favourable observations however cannot by themselves justify widespread use of fructosamine as they apply also to glycated haemoglobin (17). What then are the situations where frustosamine could have a role? In haematological disorders such as haemolytic anaemia, iron-deficiency anaemia on treatment, and haemaglobinopathies, fructosamine may be the only reliable way to assess integrated glycaemic control. Because it reflects average blood glucose over a shorter period, fructosamine may be preferred to glycated haemoglobin in situations where patients require fortnightly or montly reviews as in the management of diabetic pregnancy. Stable patients on 3-6 monthly follow-up would benefit more from glycated haemoglobin measurements. Of course it can be argued that without a knowledge of fructosamine recent metabolic deterioration could be missed. However, such deterioration, if due to secondary failure to oral hypoglycaemic agents, seldom occurs precipitously to warrant routine fructosamine measurement. On the other hand, covert omission of insulin is likely to show

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up in 2-3 weeks by a rise in fructosamine level. Hence while there is scope for its use, fructosamine should serve to complement rather than replace glycated haemoglobin, unless cost is the only consideration. At any rate, both these indices should not obviate the need for self-monitoring of blood glucose in certain groups of patients.

Studies done so far have shown that fructosamine measurements cannot as yet replace the oral-GTT for the diagnosis of diabetes. Using the NBT method, Jury (18) found that the 95th percentile of the reference range coincided with the 10th percentile of values for diabetic subjects. The diagnostic sensitivity was only 72%. By other methods, glycated proteins and glycated albumin have been found insensitive for the detection of gestational diabetes (19). Such negative findings parallel those for glycated haemoglobin (20).

In conclusion, although fructosamine is a logical corollary of the glycated haemoglobin era and a useful parameter of medium-term glycaemic control it should be used selectively. Solving some of the problems mentioned would make it more attractive. In the final analysis, whether one measures fructosamine or glycated haemoglobin, the challenge for the laboratory is how to make its results available to the doctor "on the spot" as is the case with blood glucose. This would certainly make therapeutic decisions more precise, confident and meaningful, and perhaps reduce the frequency of outpatient visits.

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